

HEART FAILURE AND DIABETES MELLITUS: WHO SHOULD BE IN CHARGE ?

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REZUMAT

Asocierea diabetului zaharat (DZ) cu insuficiența cardiacă (IC) cronică se întâlnește tot mai des în practica clinică, mai ales dacă ținem seama de prevalența crescândă atât a DZ, cât și a IC cronice, punând probleme fiziopatologice și terapeutice deosebite, atât specialiștilor în boli de nutriție și metabolism, cât și cardiologilor. Există suficiente dovezi care să ateste faptul că prezența uneia din cele două entități crește riscul de apariție al celeilalte, iar atunci când ele coexistă, riscul de morbiditate și mortalitate crește îngrijorător. În ceea ce privește tratamentul, acesta ridică probleme aparte în cazul asocierii celor două afecțiuni, mai ales dacă ne gândim că nu este foarte clar cine trebuie să conducă tratamentul, cardiologul sau diabetologul – cel mai probabil, amândoi, dacă ținem seama de particularitățile celor două patologii.

Cuvinte cheie: diabet zaharat, insuficiență cardiacă cronică

ABSTRACT

The association of diabetes mellitus (DM) and chronic heart failure (HF) is seen more often in clinical practice, specially if we take into account the increasing prevalence of both, DM and HF, with pathophysiological and therapeutic problems for specialists from the two areas, diabetologists and cardiologists. There is enough evidence to sustain the fact that the presence of one increases the risk for the other to develop, and when they coexist, the risk of morbidity and mortality is markedly increased. The treatment is more problematic for each one of the two diseases, in the presence of the other, and is not very clear who should be in charge of the treatment, the cardiologist or the diabetologist – most probably, both, taking into consideration the particularities of both pathologies.

Key Words: diabetes mellitus, chronic heart failure

INTRODUCTION

Chronic heart failure (HF) and diabetes mellitus (DM) often coexist, raising, primarily, therapeutical problems, but also regarding pathophysiological mechanisms, evolution and prognostic for the specialists in the two fields. Although diabetic cardiomyopathy shows no specific morphological features, there are altered mechanisms that can interfere with the efficiency of cardiac energy metabolism, contractile function and coupling between excitation and contraction, with cytoskeletal changes and increased neurohormonal activation, all due to hyperglycaemia. The metabolic alterations could

induce cardiac remodeling, insulin resistance playing a contributive role in the vicious circle of chronic heart failure.^{1,2}

Type 2 DM, which predominantly occurs in adults, has become increasingly prevalent worldwide. Association of an ageing population with decreased physical activity and poor dietary habits, leading most frequently to obesity, is determinant for developing and evolution of DM. At the present, 1-2% of total cardiovascular mortality is due to diabetes, but this percentage, most probably, will very soon increase.^{3,4}

DM, especially in women and in patients with asymptomatic left ventricular dysfunction, has been associated with a 3-5 fold increased risk of developing HF.^{5,6} This excess risk may be related to accelerated atherosclerosis, endothelial dysfunction, microvascular disease and autonomic dysfunction associated with diabetes.⁷ Even a moderate increase of 1% in glycosylated hemoglobin (HbA1c) leads to a more than 10% risk of HF hospitalization or death.⁸ In the Studies of Left Ventricular Dysfunction (SOLVD) trial, diabetes was a risk factor for adverse outcomes among HF patients in both the placebo and the angiotensin-converting-enzyme (ACE) inhibitor-treated groups.⁹

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Approximately 20 to 25% of HF patients are diabetics, but, if we take into account the hospitalized group of HF patients, almost 50% have diabetes.¹⁰ (Table 1)

Table 1. Prevalence of diabetes in patients with heart failure enrolled in clinical trials

Clinical trial	Patients with diabetes (%)
SOLVD (Studies of Left Ventricular Dysfunction)	25.8
MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure)	24.5
ELITE-II (Evaluation of Losartan in the Elderly)	24
Val-HeFT (Valsartan Heart Failure Trial)	25.4
COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival)	25.7
OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) (hospitalized)	44.2
VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) (hospitalized)	47

An important aspect: the natural history of HF in diabetic patients appears different, with a higher mortality especially in the case of ischaemic HF; moreover, although conventional HF treatments appear to be uniformly beneficial, in the case of ischaemic HF, the choice of the revascularization technique may differ according to diabetic status. Thus, an early, precise characterization of diabetic status should be encouraged in everyday management of HF patients.¹¹

WHAT DO WE ALREADY KNOW ABOUT THE ASSOCIATION DIABETES MELLITUS – HEART FAILURE?

About thirty years ago, Kannel and McGee reported some data on the association of diabetes and congestive heart failure and after that, an Italian study on older population with heart failure, showed that congestive heart failure is an independent predictor of type 2 DM.¹² The authors have, also, demonstrated that an increase with 1% in glycosylated haemoglobin (HbA1c), increases the risk of developing heart failure by 15%.¹³ Several studies in the last years have clearly established diabetes as risk factor for developing HF. After myocardial infarction, diabetic patients are more likely than non-diabetics to have complicated

hospital evolution, including development of HF. More recently, it has been proven that hyperglycaemia at admission because of acute myocardial infarction is a strong predictor of subsequent cardiovascular events and poor prognosis.¹⁴ Also, the risk of cardiogenic shock increases with the elevation in admission glycaemia.

But, we must not forget that diabetes-related risk factors, hypertension (HT), coronary artery disease (CAD) or left ventricular hypertrophy (LVH), all independently contribute to the development of HF.¹⁵ Further increasing the risk of HF are pathophysiological processes associated with diabetes and insulin resistance: increased central sympathetic nerve activity, endothelial dysfunction and preferential myocardial utilization of fatty acids, which may depress myocardial contractility and increase its susceptibility to ischaemic injury.^{15,16}

Endothelium-dependent vasodilation is substantially impaired in diabetic patients. The generation of increased vascular production of superoxide contributes to this impairment of endothelium-dependent vasorelaxation.

Superoxide is involved, also, in the oxidative modification of low-density lipoprotein induced by glucose concentrations occurring in the diabetic state. Another relevant mechanism involves direct inactivation of endothelium-derived relaxin factor (EDRF) by advanced glycosylation products and increased adhesion of leucocytes to the endothelium.¹⁷ The source of vascular oxygen-free radicals in diabetes is not very clear. Interestingly, the treatment of insulin-dependent diabetics with an ACE inhibitor improves endothelium-dependent vasorelaxation as measured by changes in forearm bloodflow upon intrabrachial infusion of acetylcholine, so, induction of vascular oxidases by angiotensin II and subsequent production of superoxide and peroxynitrite might, also, play a role in diabetes.¹⁸ The last two mentioned substances are important mediators of pancreatic cell death; they might serve as pathogenic precipitating factors.¹⁹

On the other hand, HF itself increases the risk of insulin resistance and diabetes. The mechanisms that may promote the development of insulin resistance in HF include sympathetic nervous system activation and elevated circulating free fatty acids.²⁰

HEART FAILURE

If we take only HF *per se* into account (for pure theoretical reason), we define it as a complex syndrome, recognized through multiple symptoms and clinical signs, produced by any cardiac dysfunction, structural

or functional, which affects the filling or the ejection ventricular capacity, as it is defined in the ACC/AHA Guidelines from 2001.²¹

When we talk about HF, we have to keep in mind that HF is a symptomatic dysfunction, but not always (because there are forms of HF with no clinical signs or symptoms, at least not in the early stages), and a progressive dysfunction, the most common manifestation of this evolving dysfunction being the alteration of the ventricular/cardiac geometry.^{22,23}

Symptomatic dysfunction – the mechanisms responsible for effort intolerance in patients with chronic HF aren't well known. Many studies have already shown that there is no well defined relation between cardiac performance and clinical manifestations. There are patients with very low ejection fraction who are asymptomatic or very poor symptomatic, and, on the other side, patients severe symptomatic, but with preserved systolic function. The mechanisms involved in this process, that could explain this, are: alteration in ventricular distensibility, valvular regurgitation, pericardial restriction and the function of the right ventricle.

Progressive dysfunction – left ventricular dysfunction starts from one myocardial lesion or from myocardial stress, but after that, it is a progressive, evolving process, even without any other identifiable cardiac cause. The main feature of this evolving dysfunction, is the alteration of the left ventricular geometry, with chamber dilation and hypertrophy, the ventricle becoming more spherical – we are dealing with **ventricular remodeling**. This will increase hemodynamic stress on the walls and will reduce cardiac performance, but, in the same time, will increase the degree of mitral regurgitation and, consecutive, will augment the remodeling process. Usually, the ventricular remodeling precedes clinical signs (with a few months, or, even, a few years), continuing after their appearance, contributing to cardiac performance alteration, in spite of the correct medical treatment.

The factors contributing to cardiac remodeling are already known: norepinephrine, angiotensin II, aldosterone, endothelin, vasopressin, cytokines, all neurohormonal agents that increase hemodynamic stress by fluid and salt retention and systemic vasoconstriction, but, also, have a direct cardiac toxic effect and stimulate myocardial fibrosis, with consecutive alteration in myocardial architecture and more reduction in cardiac performance.²²

And another important aspect: the dilated, failing heart is energetically ineffective!

We will not insist on the essential pathophysiological mechanisms in HF, they are well known

by now (structural cardiac alterations: β -adrenergic desensibilization, hypertrophy, necrosis, fibrosis or apoptosis; left ventricular remodeling; inflammation and obstruction of coronary arteries; functional alterations: mitral regurgitation, intermittent ischaemia or hibernating myocardium, atrial or ventricular arrhythmias; biological active factors: RAAS, SNS, vasodilative substances, natriuretic peptides, cytokines, vasopressin, metalloproteinase-matrix; other factors: age, gender, genetic factors, smoking, alcohol consumption, environmental factors; associated pathological conditions: hypertension, diabetes, nephropathies, anemia, obesity, sleep apnea syndrome, depression, coronary artery disease etc.), but, they are important to be mentioned and, much more, to be known, because of their implications in the choice of treatment in HF.

Maybe we should remember that two of the most important risk factors for development of HF in epidemiological studies are CAD and hypertension, but are not the only risk factors. An example: increased body mass index (BMI) represents an independent risk factor for the development of HF - a 2.5 unit increase in BMI determines an increase in the risk of HF by 12%.²⁴⁻²⁶ The list goes on with the other important risk factors, already well known – increasing age, coronary heart disease, hyperglycaemia, nephropathy, proteinuria, end-stage renal disease, retinopathy, use of insulin or duration of diabetes. These data have, also, important relevance in the treatment's choice.

The stadialization of HF permits us to recognize a similarity between HF and coronary artery disease: they both present risk factors and structural predisposing features, the evolution has symptomatic and asymptomatic periods and specific treatment of each stage may improve the morbidity and mortality.²⁷ It is of no relevance what the cause of HF is, because the systemic response and the structural alteration that appear as a response to the initial injury, are the same!

DIABETES MELLITUS

When we refer to diabetes in relation with heart failure, we must remember that diabetes promotes development of cardiomyopathy, independent of hypertension and CAD, through direct effects of hyperglycaemia and insulin resistance on the heart. In fact, three of the most important risk factors, CAD, hypertension and specific diabetic cardiomyopathy, are the most common etiologies of HF in diabetic patients (for which Bell used the term "cardiotoxic triad").²⁸

But, the high prevalence of HF in diabetic patients cannot be explained just by the presence of traditional risk factors. Alterations in left ventricular function were observed in more than 50% of diabetic patients (with type 1 or type 2 DM). Diastolic dysfunction is often present in young diabetic people, otherwise, apparently 'healthy people', without additional cardiovascular risk factors. For some years now, this myocardial impairment in patients with DM is defined as **diabetic cardiomyopathy** and can vary from clinically asymptomatic forms to symptomatic impairment of myocardial performance, due to fibrosis, altered calcium homeostasis (they represent the end of the chain of accumulation of advanced glycation end-products in the myocardium), increased wall stiffness, restrictive ventricular filling with global hypokinesia. Additional cardiotoxic effects of hyperglycaemia and insulin resistance include: cardiac hypertrophy, endothelial dysfunction (an imbalance between arterial response to vasoconstrictors and vasodilators), inflammation and lipotoxicity.²⁴ Endothelial dysfunction, present in patients with HF, has, as a matter of fact, many causes, the most important being the local elevation in the level of angiotensin II and endothelin.

But, interestingly, none of the known morphological alterations in the diabetic heart (myocyte hypertrophy, deposition of glycoproteins, interstitial oedema, accumulation of extracellular matrix, loss of myocytes, which are substituted by interstitial connective tissue, vascular abnormalities, like thickening of arterial intima or microaneurysms formation) are specific, so, we must take into account the fact that we have to deal with an alteration at another level: functional, biochemical or both!

A few years ago, the UKPDS trial showed that the incidence of HF is high in patients with poor glycaemic control.²⁹ After that, another trial, with a follow-up period of 2 years, on 49 000 patients with type 2 diabetes, observed an increase of 8% in the risk of developing HF for every 1% elevation in HbA1c. More recently, new data show that glycaemia represents a risk factor for heart failure even in patients who are not known as diabetics. In a substudy of RESOLVD, from 663 patients with HF, functional NYHA class II-IV, 27% had documented DM, but from the non-diabetics, 11% met diagnostic criteria of DM, 12% had impaired fasting glucose (IFG) and 34% had elevated plasma insulin levels and insulin resistance.³⁰ Insulin resistance, in the absence of DM, represents an independent prognostic factor of HF.³¹

Diabetes predicts, as we have mentioned already, poor outcomes in patients with established HF. DM represents a risk factor for progression

from asymptomatic left ventricular dysfunction to symptomatic HF (RR=1.6 in SOLVD) and, also, a risk factor for all-cause mortality (RR=1.4 in SOLVD), but, with the mention that this increased risk was observed only in patients with ischaemic etiology of HF.^{32,33} An increased mortality risk associated with diabetes has been observed in other HF groups, including elderly patients with chronic and new-onset HF and, also, advanced HF in a transplant referral center.^{34,35}

TREATMENT PARTICULARITIES IN PATIENTS WITH HEART FAILURE AND DIABETES

HF treatment has considerably improved in the last 20 years. If in the 80's we talked only about a symptomatic treatment, in our days the utilisation of ACE inhibitors (ACEI), of angiotensin receptor blockers (ARB), of β -blockers and aldosterone antagonists, brought major benefits in clinical improvement, in the well-being of the HF patients and, not least, in the survival rate of these patients. When these neurohormonal agents are administrated in the early stages of heart failure, if possible, asymptomatic stages, the development of symptomatic HF could be prevented or delayed! The benefits rise considerably when these agents are given together and not as monotherapy. All four therapeutical classes exert a positive effect on cardiac remodeling, an essential element in the progression of HF.

Both HF management guidelines, ESC (European Society of Cardiology) and ACC/AHA (American College of Cardiology/American Heart Association), took into consideration all the data from the clinical trials that were conducted in the last years on patients with HF ("evidence-based medicine"). Thus, if the guidelines from 1997 mentioned as mandatory treatment with ACEI in all stages of HF, including asymptomatic dysfunction of left ventricle, β -blockers being recommended only in the mild and moderate stages of HF, the 2001 version of the ESC guidelines, broadened the spectrum of indications for β -blockers to all symptomatic stages of HF, including LV dysfunction post-myocardial infarction, introduced the recommendation to use aldosterone antagonists in the advanced stages of HF and angiotensin receptor blockers (ARB) in case of ACEI intolerance.^{36,37} In 2005 the new guidelines came with the recommendation to associate ACEI and ARB in the treatment of mild and moderate HF.³⁸ In the last years, an important message was transmitted: in the absence of fluid retention, ACEI, and not diuretics, should be preferred as first line therapy in HF. And another major indication: all

Table 2. Effects of ACE inhibitors on mortality in diabetic and non-diabetic patients with heart failure.

Trial	Patients (N)	Non-diabetic (N)	Diabetic (N)	RR, non-diabetic (95% CI)	RR, diabetic (95% CI)	RRR (95% CI)
CONSENSUS	253	197	56	0.64 (0.46-0.88)	1.06 (0.65-1.74)	1.67 (0.93-3.01)
SAVE	2,231	1,739	492	0.82 (0.68-0.99)	0.89 (0.68-1.16)	1.09 (0.79-1.50)
SMILE	1,556	1,253	303	0.79 (0.54-1.15)	0.44 (0.22-0.87)	0.56 (0.25-1.22)
SOLVD-Prevention	4,228	3,581	647	0.97 (0.83-1.15)	0.75 (0.55-1.02)	0.77 (0.54-1.09)
SOLVD-Treatment	2,569	1,906	663	0.84 (0.74-0.95)	1.01 (0.85-1.21)	1.21 (0.97-1.50)
TRACE	1,749	1,512	237	0.85 (0.74-0.97)	0.73 (0.57-0.94)	0.87 (0.65-1.15)
Random effects pooled estimate		10,188	2,398	0.85 (0.78-0.92)	0.84 (0.70-1.00)	1.00 (0.80-1.25)

the last guidelines underlined the need in use of certain doses of the recommended agents, with progressive adjustments until the target doses, the efficient doses, have been achieved.

The guidelines reflect the international consensus on the most efficient way to treat a patient, based on the experts opinions and on the data from clinical trials, which means that the impact on clinical day-to-day practice should be major! But it isn't so!

It was observed that the number of HF patients treated according to the recommendations of the guidelines is much less than expected, far from being optimal. Unfortunately, this is the case not only with HF, but, also, with hypertension or coronary artery disease! It has been, also, noticed that the administered doses are far from those recommended.

The essential objectives in the treatment of HF with systolic dysfunction (prevention of the evolution from underlying disease to diastolic and/or systolic dysfunction, prevention of the progression to symptomatic HF, preservation and improvement of quality of life, survival improvement) are the same if we talk about diabetic HF patients, but with more considerations taken into account, related to diabetes itself.

We must not forget the importance of lifestyle changes, especially when we refer to diabetic, HF patients. No medical treatment has benefit, if the lifestyle changes are not followed.

What does medical evidence tell us? That, indeed, diabetic HF patients benefit from standard, life-prolonging HF medical therapy.

In a meta-analysis of 6 randomized, controlled trials of ACE inhibitors (ACEI) in systolic HF, including 2,398 diabetics and 10,188 non-diabetic subjects, Shekelle and his colleagues found that ACEI

therapy was associated with a 14%, respectively 15%, decrease in mortality risk.³⁹ (Table 2)

In MICRO-HOPE, Ramipril lowered the risk of developing HF in 3577 diabetic patients by 20% ($p=0.019$), while in PERSUADE (EUROPA substudy), Perindopril determined a 46% relative-risk reduction in first HF hospitalization (yet, not statistically significant) in 1502 diabetic patients.^{40,41} Based on the guidelines of ESC (European Society of Cardiology) and EASD (European Association for the Study of Diabetes) from 2007, ACE inhibitors are recommended as first-line therapy in diabetic patients with reduced LV function, with or without symptoms of HF (class I, level of evidence C).⁴²

In CHARM trial, Candesartan reduced the incidence of DM in patients with HF: from 5436 patients without DM at randomization, 202 (7.4%) in the placebo group developed DM vs 163 patients (6%) in the Candesartan group ($p=0.02$).⁴³ In IDNT, 1715 diabetic patients with nephropathy, randomized on Irbesartan, Amlodipine or placebo, Irbesartan reduced the incidence of HF, compared with placebo ($p=0.048$), while in LIFE, Losartan reduced the risk of first hospitalization for HF in diabetic patients, compared to Atenolol ($p=0.019$).⁴⁴ Angiotensin II receptor blockers (ARBs) have similar effects in HF as ACE inhibitors and can be used as an alternative or even associated treatment to ACE inhibitors (class I, level of evidence C).⁴²

There is abundant clinical evidence to support the use of β -adrenergic antagonists to reduce morbidity and mortality in diabetic patients with systolic heart failure. A pooled analysis of three randomized controlled trials, which included 1,883 diabetic and 7,042 non-diabetic HF patients, demonstrated a huge benefit from β -blockers in the two groups of patients

(39). In COMET (Carvedilol or Metoprolol European Trial), the subgroup of diabetic HF patients had improved risk reduction with Carvedilol compared to Metoprolol, on similar scale as non-diabetic patients (RR: 0.85 for diabetic patients and 0.82 for non-diabetics).⁴⁵ One remark: β -blockers may be underutilized in diabetic patients with heart failure, due to the concerns about worsening of insulin resistance and dyslipidemia, development of hypoglycaemic unawareness or exacerbation of erectile dysfunction. But, severe hypoglycaemia is extremely rare in type 2 diabetes. Beneficial effects of the vasodilating β -blockers include improved insulin sensitivity, decrease in the level of triglycerides, improved renal blood flow and reduction of albuminuria. β -blockers (Metoprolol, Bisoprolol, Carvedilol) are recommended as first-line therapy in diabetic patients with HF (class I, level of evidence C).⁴²

Aldosterone antagonists represent a standard life-prolonging class of drugs in the treatment of HF. In RALES trial, there was a 30% reduction in mortality risk in 1,663 patients with systolic HF, with NYHA class III-IV, on Spironolactone (but, there was no report on diabetic subgroup).⁴⁶ In the EPHEsus trial on 3,319 post-myocardial infarction patients, with left ventricular dysfunction, there was a 15% reduction in mortality risk with Eplerenone, and risk reduction was important in the two subgroups, diabetics and non-diabetics.⁴⁷ The risk of developing hyperkalemia in this two trials was low (2% and 5.5%, respectively), but, usually, the frequency of hyperkalemia in diabetics, especially if they have renal dysfunction, may be higher.⁴⁸

Prevention of hyperkalemia in high-risk patients involves initiation with low doses, longer maintenance of an established dose, frequent monitoring of renal function and electrolytes, concomitant loop diuretic therapy, restricted dietary potassium. Anyway, aldosterone antagonists may be added to ACE inhibitors, β -blockers and diuretics (loop diuretics) in diabetic patients with severe HF (class IIb, level of evidence C).⁴²

In TNT, where patients with CAD, were randomized to Atorvastatin 80 vs 10mg/day (1,501 being diabetics), the higher dose of statin reduced significantly first hospitalization for HF in diabetics and non-diabetics.⁴⁹ But, in ASCOT-LLA, in diabetic patients, there was a non-significant trend towards reduction in HF with Atorvastatin 10mg/day.⁵⁰ One year ago, guidelines on diabetes, pre-diabetes and cardiovascular diseases from ESC and EASD mentioned that statins should represent first line therapy in diabetic patients (class I, level of evidence

A) and all diabetic patients with type 1 of DM, over 40 years old, should receive statin therapy. Patients between 18 and 39 years old, with type 1 or type 2 DM, should receive statins in the presence of other risk factors (nephropathy, poor glycaemic control, metabolic syndrome, atherosclerosis manifestations) (class IIb, level of evidence C).⁴⁰ With all the controversial data from last clinical trials, taking into account all their beneficial effects on well established mechanisms, with careful monitoring, we really think that we mustn't deprive diabetic patients with HF with associated risk factors, from this therapeutic class.

Concerning the device therapy for HF (implantable cardioverter defibrillators - ICD, cardiac resynchronization therapy - RCT), they both reduce morbidity and mortality in certain subsets of HF patients, but the major device clinical trials did not include analyses for the subgroup of diabetic patients. So, device therapy is indicated for diabetic HF patients who meet established criteria for ICD or RCT.

The medical treatment for DM determines improved glycaemic control, with beneficial effect in HF (improvement of myocardial glucose utilization and decrease of free fatty acids).

ADA and EASD consensus statement recommends using an algorithm that promotes the preferential use of older agents, including metformin, sulfonylureas and insulin. This algorithm takes into account the evidence for HbA_{1c}-lowering for each agent, the synergistic effects of multiple agents and cost-effectiveness report.⁵¹

Sulfonylureas are still frequently used in diabetics with HF, even though they stimulate endogenous insulin production, which is not a particularly rational approach in insulin resistant states of DM and HF.

The ADA guidelines established that Metformin is contraindicated in patients with HF, due to concerns about lactic acidosis. But, in fact, Metformin is used on a large scale in HF and incidence of lactic acidosis is not very high. Lactic acidosis, a potentially fatal adverse effect, is extremely rare and is associated, almost exclusively, with other risk factors (renal or hepatic disease). So, metformin is contraindicated in patients with moderate and severe renal failure (plasma-creatinine levels $\geq 1.5\text{mg}\%$ in men and $\geq 1.4\text{mg}\%$ in women).

Guidelines from 2007 (ESC/EASD) established that insulin treatment in patients with DM and HF is under debate. It might have beneficial effects on myocardial function, but it could be associated with increased mortality.³³

Meglitinides stimulate insulin secretion by binding to the sulfonylurea receptor, have a more rapid onset

and shorter duration of action than the sulfonylureas and are designed to target postprandial hyperglycemia.

Thiazolidinediones, insulin sensitizers used as glucose-lowering drugs in the treatment of diabetes, represent a controversial treatment in HF patients, due to the risk of fluid retention, with decrease in haemoglobin and haematocrit, with oedema and weight gain (about 1-3 kg), with worsening of HF symptoms. When combined with Insulin, the rate of oedema increases even more.

In a recent meta-analysis from seven randomized controlled trials, including 20,191 patients treated with Pioglitazone or Rosiglitazone, in comparison to controls, patients treated with thiazolidinediones had an increased risk of HF (RR=1.72), but this was not associated with increased risk of cardiovascular death (RR=0.93). Until 2008, it was stated that thiazolidinediones shouldn't be administered in HF class III-IV NYHA (where they are contraindicated), but they may be attempted in HF patients with milder degrees of HF (class NYHA I-II).⁴² But, from this year, they are contraindicated even in classes I and II NYHA of HF.⁵¹

Omega-3 fatty-acid supplementation improves morbidity and mortality in diabetic symptomatic HF patients.⁵²

The other classes of oral antihyperglycaemic agents (α -glucosidase inhibitors, glucagon-like peptide-1 analogues, dipeptidyl peptidase IV inhibitors, amylin mimetics) keep their recommendations in diabetic patients, usually, based on the advice of diabetologist.

All these are just a few reminders of the complex challenging treatment of heart failure associated with diabetes. From case to case, we have to individualize every approach, taking into consideration the particularities of each particular patient (hypertension, coronary artery disease, arrhythmias, significant dyslipidemia, comorbidities associated, that, maybe, will restrict our choice of treatment, retinopathy, nephropathy, chronic kidney disease or end-stage renal failure etc.).

CONCLUSION

The remaining question is: who should manage patients with heart failure and diabetes? And the answer should be, judging from our experience, cardiologists and diabetologists together! They have to cooperate, to offer to heart failure diabetic patients, optimal medical (and not only) treatment (recommended drugs and target-doses), for heart failure, and also for diabetes, and to monitor their combination regarding the eventual adverse events.

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